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William Edgar Lower, M.D.

1867 - 1948

Founder Member

Memorial Issue

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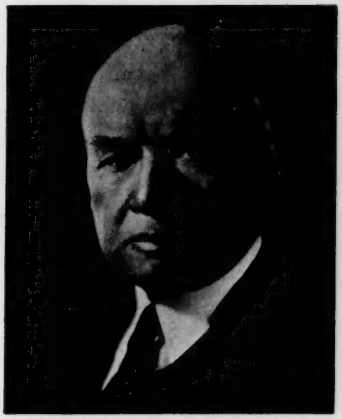
MEMORIAL SERVICE

ON June 26, 1948, a memorial service for Dr. William E. Lower was held at the Cleveland Clinic. Mr. John Sherwin, President of the Board of Trustees, presided. The Tributes which follow were given by Dr. Winfred G. Leutner, President of Western Reserve University, Dr. Norman C. Tarian, former President and Chief of Staff of the Lutheran Hospital, Dr. Thomas E. Jones, Chief of Staff of Surgery at the Cleveland Clinic, and Dr. William F. Braasch of the Mayo Foundation.



JOHN SHERWIN . . .

ON June 17, 1948, the last survivor of the four founders of The Cleveland Clinic Foundation, Dr. William E. Lower, passed away at the age of eighty-one, having lived a full life devoted to the alleviation of human suffering and misfortune. Loved and respected by all those who had the privilege of coming within the sphere of his influence, he has left a host of friends and admirers in all walks of life who will miss his kindly word and helping hand.

His contribution to the advancement of his profession is well known to all its members. His contribution to the Cleveland Clinic, both professionally and through the part he played in guiding its progress from the concept of the idea to the present time, is evident in the character of the institution itself and in the indelible mark his personality has left on it.

This issue of the Cleveland Clinic Quarterly is dedicated to the memory of Dr. Lower to permanently record the thoughts and reminiscences presented at that service.

DR. WINFRED G. LEUTNER . . .

AS a young surgeon Dr. Lower interested himself in the late '90's in the foundation and operation of a new and modest hospital venture on the west side, the now well-known Lutheran Hospital. I refer briefly to it because it brought Dr. Lower first within the orbit of my own youthful experience.

Dr. Lower had graduated as a Doctor of Medicine from the School of Medicine of Wooster University in 1891. The consolidation of that School five years later with the School of Medicine of Western Reserve University enrolled him among the alumni of the University. His professional work as a member of the faculty of the School of Medicine began in 1898 as lecturer and continued

until 1931 when he retired from the faculty with the rank of Associate Professor, a period of thirty-three years. His surgical career included appointments in Lakeside Hospital and Mt. Sinai Hospital.

In the meantime he had as early as 1900 become an army surgeon, an activity in which he was to play a major role. He served first in the Philippines and then became a major in the Medical Reserve Corps. He was called to active service in 1917 as Assistant Surgical Director of the Lakeside Base Hospital Unit of the United States Army in service with the British Expeditionary Forces in France. For a time he was its commanding officer and retired with the rank of Lieutenant Colonel in 1918.

As is well known, the idea of establishing the Cleveland Clinic Foundation Hospital had long been discussed by Doctors Crile, Lower and Bunts, and in 1921 Dr. Lower became one of the founders of the Foundation and Chief Surgeon of the Cleveland Clinic Hospital. The role that he played from the beginning in planning, in building and in organizing the working forces of the Cleveland Clinic and its Hospital is too well known to warrant detailed account here. I think it is fair to say that the team of Dr. Crile and Dr. Lower with their associates—Bunts, Phillips, and their colleagues—brought into the service of the sick a force destined to make an extraordinary contribution to the medical and surgical care from wide areas of the population of the United States and even outside the limits of our country.

The most difficult problems of organization, of buildings and of maintenance which might well have discouraged one with lesser faith, especially when disaster threatened, Dr. Lower faced always with calmness and quiet cheerfulness that was as amazing as it was disarming. Indeed, the Cleveland Clinic Foundation and the Hospital became his life, and through them he made to this community and to the world a contribution such as few men are privileged to make.

As friends and associates we deeply mourn his departure. The entire community is the poorer for his passing, but we are proud to nurture his memory, and to continue to push forward in the direction of his ideals and to count him in the long years ahead as one of God's gifts to our generation.

Dr. Norman C. Yarian . . .

TO have known and to have worked with Dr. William E. Lower has been one of the richest and most valuable privileges of my life. I came to know him fifty-three years ago, when as a student-assistant I entered the offices of Drs. Bunts, Crile and Lower.

Some of Dr. Lower's characteristics which impressed me most were kindliness, consideration for others, sincerity, devotion to his profession and his interest in helping young men. I am sure that many physicians, like myself, owe more than they can express for his interest and helpfulness. The sole criterion in his decisions was the welfare of the patient.

He was one of the most tireless physicians I have ever known. Busy from early morning until late at night, he knew no eight hour day, and he usually kept his appointments ahead of schedule, as many of us can attest.

In the earlier days of his practice, it was not unusual for surgical operations to be performed upon the kitchen table in a poorly lighted room in the patient's home. I recall such experiences, having either served as anesthetist or assistant, and despite the unfavorable setting for the operation, Dr. Lower's patients usually made a good recovery.

But it was when witnessing intubations upon children nearly suffocated from laryngeal diphtheria that he impressed me most. These intubations were often done at night, the doctor having been called from his sleep to the bedside of a child rapidly becoming cyanotic for want of air because of the terrible diphtheria membrane closing his larynx. Dr. Lower was there at his best. As one of us held the child, wrapped in a sheet, he dexterously introduced the tube into the larynx and in a few moments the cyanosis was gone and the child fell into a restful sleep. Dr. Lower's reputation for doing intubations was widely known and many children's lives were saved by his skill. He operated in numerous hospitals in the city as well as in other cities where he was called in consultation.

I vividly remember night trips I made with him behind his faithful mare, Lucy, to the Cleveland General Hospital (long since gone from Woodland Avenue), in response to some emergency call. Our quiet conversations in the flickering lights of the city as we drove down old Hick Street and over the Central Viaduct, lives on as a choice memory.

He was one of the first surgeons to operate in the White Hospital at Ravenna. It has been my privilege to have witnessed much of his work at the Lutheran Hospital, founded in 1896, the year of my graduation in medicine. Dr. Lower not only exerted a great formative influence in establishing the institution but always aided in upholding a high standard of the work done there. This interest continued as long as he lived.

We of the staff of the Lutheran Hospital have always held him in the highest regard and respect. He was our President and Chief-of-Staff for twenty-two years. We shall greatly miss his words of counsel and encouragement but his influence will live on. His framed photograph hangs upon the wall of the doctors' room in the hospital, just as it has hung beside my own desk for many years, and will remain there so long as my office continues.

DR. THOMAS E. JONES . . .

AFTER a long association with Dr. Lower which began after World War I in the office of Bunts, Crile and Lower in the Osborn Building, I find it difficult to do justice in representing the Staff in this memorial service to Dr. Lower, the last of our Founders to depart. When one is closely associated with a person for many years it is impossible to properly appraise him. So

many things are taken for granted in day by day communion that sometimes the great things are overlooked. When the final parting comes, one's emotions are likely to be expressed in superlatives, and that is the last thing Dr. Lower would want, contemptuous as he was in the presence of gallery play.

On occasions in the past I have paid tribute to our Founders: to Dr. Bunts, the gentleman and scholar, the mediator and friend; to Dr. Crile, always the stimulator who blazed the trail for anyone who wished to follow; to Dr. Phillips who was to everyone the ideal doctor, and now to Dr. Lower.

Today this institution is a monument to Dr. Lower's wisdom and planning and scrupulous attention to economy. He liked to plan, construct and complete—then be off to another job.

Time does not permit even a brief recital of his achievements and the honors bestowed on him in recognition of them. They are a matter of record elsewhere. It is an imposing summary but inadequate. One does not find here the secret of the irresistible personal magnetism which so endeared him to a host of colleagues, friends and grateful recipients of his professional skill. This was found in the collective attributes of his personality. He was gracious, humble, richly endowed with intellect, sound judgment and firm convictions, and in retrospect they were all consecrated to the service of humanity. The motivating force that activated his many virtues was a consuming and sustained desire to serve his fellow man modestly and efficiently, and to relieve suffering. Completely subservient to this was conventional social intercourse in which he had little interest, yet on any occasion he was a charming host, both at home and on the farm which furnished his chief recreation. He was courteous without formality. He took great delight in horseback riding and in the study of trees, birds and wild flowers.

Directness of speech and thought was one of Dr. Lower's characteristics and there was never a question as to where he stood on a problem. His art of conversation linked with a gift of repartee and sense of humor made an impression not easily forgotten. He was a skillful surgeon, bold when necessary but not adventurous. He had that rare ability to apply his native talents in a manner that successfully combined his analytical mind, dexterity and common sense. He gave dignity to the operating room and to surgery without any pretentious solemnity.

His aim in writing was, like his oral technic, chiefly directed at lucidity, brevity and correctness without display of ornamental bibliographic erudition.

One of his outstanding traits was punctuality and he could not countenance tardiness in others. I am reminded of an annual Clinic meeting and a verse of a song which was as follows:

> "There's no one at the Clinic who hasn't had the fate
> To meet the next speaker at the door when he is late.
> He checks us up each morning; one's faults he knows too well.
> We hope we have some virtues, too, of which he'll also tell."

With his natural quick wit he responded, "Of course I can't conceive of any one being late, but I can readily imagine, should one be late, how dis-

tressed he would feel, and so I hope I may continue to be at the door to comfort him as he comes in."

His spirit was always free, alert and vivacious. He was cheerful and kind to his patients and had the happy knack of friendliness for rich and poor, young and old, learned and ignorant. In my long association with Dr. Lower, I have never seen a trace of conceit or boastfulness.

He had his fun, however. Raised on a farm in Ohio and educated in a country school, he grew up the hard way, and when he came to Cleveland could hold his own with the "city slickers." One gleaned from stories by Dr. Crile and Dr. Bunts that he was more bent on mischief than books, but when his interest in medicine began he became as absorbed with the single idea of doing a day's work as honestly, faithfully and energetically as was in his power. Nor did he fail to prod others as many of us are aware. When I joined the old group of Bunts, Crile and Lower, occasionally I would meet some of his cronies who had lived with him at the old University Club on Prospect Avenue. Invariably they would say, "Old Billy Lower is quite a boy." He was a prankster. He enjoyed real fun that hurt no one but may have caused some annoyance to the victim of the joke. We are told that the recipient of many of these was former Justice Clarke of the Supreme Court. In spite of this they were loyal friends and frequently corresponded until the latter's death a few years ago. Dr. Lower told stories well, particularly when the joke was on himself. With advancing age one is apt to spend a lot of time reminiscing, but Dr. Lower did not; he always looked toward the future and its probable accomplishments.

He told me many times that he had tried his hand at reforming but eventually gave it up. Perhaps that accounted for his ability to avoid insoluble issues successfully and gracefully in a few well-chosen words. He never prophesied but he was a visionary. Well do I remember the controversy twenty years ago when he took up vigorous defense against the so-called higher education for nurses. It was misinterpreted. Dr. Lower would not deny education for anyone but he felt that many people were denied the opportunity to serve. From his early association with Lutheran Hospital he knew full well the qualifications of a nurse and he did not think a college education was necessary to fulfill the requirements and that it would militate against the training of much real talent.

Dr. Lower established a library at Coshocton, Ohio, in memory of his nephew, Hunter Lower, and also one in memory of his father and mother, known as the Henry and Mary Lower Fund. In giving these libraries he specified that they were to be used only for nature and scientific subjects. He also established a fund for the Lower Fellowship Thesis prize. He was the donor of the Lower Lecture and a permanent fund has been set up to perpetuate this at the Academy of Medicine—such was his interest in education.

One of his greatest traits was probably least known. Things do not always progress serenely in any institution and particularly in a rapidly growing one. We are apt to get fractious in times of stress and over-work, and many were the complaints he had to face. However unruly, in his presence you were soon

subdued; he bridled and saddled you and the cinch was adjusted to proper tightness before you returned serenely onto the track.

These words of Robert Louis Stevenson may fittingly be applied to the life of Dr. Lower and the Clinic for which he worked so hard:

"Our road is not built to last a thousand years, yet in a sense it does. When a road is once built it is a strange thing how it collects traffic, how every year as it goes on more people are found to walk on it and others are raised up to repair it and keep it alive."

In a large measure he has been responsible for a potent ferment with which we are now endowed and I am sure it is his wish that it continue to effervesce to the benefit of all. We have an obligation to guard it wisely. The road of knowledge, skill and character which he built will be kept alive by the gratitude of the patients he served, the accomplishments of the students he taught, and the affectionate memories of the colleagues to whom he was an inspiration and an example.

Wherever "Billy" Lower is today, he is at peace. He was so true to his convictions.

DR. WILLIAM F. BRAASCH . . .

MY acquaintance with "Billy" Lower began in 1907. At that time American urology was in the embryonic stage of its development. There were only three or four specialists in that field west of the Atlantic Coast. Since my knowledge of urology was limited, Dr. W. J. Mayo (the Chief) advised me to spend some time with Dr. Lower in Cleveland, saying that in his opinion he was the leading American urologist of that day.

When I arrived in Cleveland, Dr. Lower welcomed me with unassuming charm and warmth of personality. He was a bachelor at that time and, in his friendly way, suggested that I share his quarters. I shall never forget the wonderful weeks spent with him, making daily rounds, watching him work, and listening to his wise words of counsel. He had an electric automobile then and I can still see him as he drove the car to the various hospitals where he worked, commenting on medical conditions and problems as he drove.

What I learned from him at that time was a large factor in guiding my subsequent progress in urology and in laying the foundation for the Section on Urology at the Mayo Clinic. I know that the same generosity he showed to me as a teacher was extended to many other young urologists. It is evident that it gave him pleasure to be of help to his younger colleagues.

Dr. Lower was fundamentally a surgeon. He belonged to that remarkable group of Americans who contributed so much to the surgical field during the first two decades of this century. These men will go down in surgical history because of their influence in simplifying and standardizing the technical procedures of surgery and in shaping them as they exist today. Dr. Lower demonstrated the value of speed with surgical dexterity and sound surgical judgment.

He possessed the three cardinal virtues of a modern surgeon to a superlative degree. While in no way oratorical, the eloquence of his keen observations at the operating table or bedside made a deep impression on the minds of those who heard him.

Dr. Lower was widely known as an outstanding general surgeon but he was particularly interested in the field of genito-urinary surgery. He took a keen interest in the problems of urology and contributed generously to that field. He was among the first of the urologists to perform suprapubic prostatectomy and to advocate bilateral transplantation of the ureters for exstrophy of the bladder. He made improvements in various operative technics and described a number of instruments to aid in their application. As an example of his breadth of vision and his forward looking manner of thought, in his later years he actively encouraged research in the basic sciences in order to solve various problems in urology. His contributions to the subject of hypophyseal gonadal influence on the growth of the prostate gland were important and stimulated additional research.

He conceived and helped establish the Clinical Society of Genito-Urinary Surgeons and served in the capacity of President in 1921 and 1922. He was also keenly interested in the affairs of the American Association of Genito-Urinary Surgeons and was President in 1923. Whenever Dr. Lower read or discussed a paper, he commanded profound attention. In fact, his discussions of various urologic problems were so informative and were based on such wide experience and keen observation that they were always remembered.

In addition to Dr. Lower's attributes as a surgeon and urologist, there was a quality in his clinical work which was outstanding: his humanitarian interest in the patient himself. This permeated his every thought and action. In his quiet way, with the aid of his kindly smile and humorous remarks, he gained his patient's confidence.

Dr. Lower left a heritage to the surgical world and in particular to urology, which will continue to influence it as profoundly in the future as in the past. Those of us who were fortunate enough to come in contact with him will always remember him as a great teacher, a great clinician, a good doctor and a kind friend.

TYPES OF ESSENTIAL HYPERTENSION AND THEIR RELATIONSHIP TO THERAPY*

ALYS LIPSCOMB, M.D.
Fellow in Medicine

STATISTICS[1] show that more than 500,000 persons in this country die each year as a result of hypertensive vascular disease. It has been estimated that hypertension affects 20 to 40 per cent of the population.[2,3] This implies that there is no consistently effective therapy for high blood pressure in spite of the numerous reports of medications, dietary schedules and surgical procedures, each of which is reported to give good results in 50 to 85 per cent of patients. In 1929 Ayman[4] listed 200 separate remedies which had been recommended during the preceding decade. The table lists 8 widely diverse treatments offered in the past twenty-five years. The favorable results reported are comparable. A rational explanation of why psychotherapy, oral ingestion of thiocyanates, restriction of dietary sodium and operations upon the sympathetic nervous system should exact similar physiological responses is obscure. The only obvious possibility is that some hypertensive persons respond to attention and care in the same way regardless of "specific" treatment. If this is the correct interpretation all statistics will be difficult to construe unless this factor can be eliminated.

TABLE

Therapy	Author	Date Published	Per Cent Patients In Whom Blood Pressure Was Lowered
Low Sodium	Allen, F. M. et al.	1922	61
	Selman	1923	60
	Allen, F. M.	1925	60
	Vogel	1928	74
	Grollman et al.	1945	66
	Bryant et al.	1947	76
(Rice Diet)	Kempner	1944-1945	64
Psychotherapy	Buck	1937	66
Liver Extract	MacDonald	1927	60
Watermelon Seed Extract	Wilkinson	1927	82
	Althausen et al.	1929	73

**Lower Fellowship Prize Thesis, 1948, condensed. Robert D. Taylor, M.D., advisor*

Thiocyanate	Nichols	1925	66
	Bolotin	1932	68
	Barker	1936	50
	Kurtz et al.	1941	78
Phenobarbital	Gruber	1925	85
Sympathetic Nervous System Surgery	Craig et al.	1939	52
	Smithwick	1947	66
	Peet et al.	1946	81

Differentiation of known causes of hypertension is important. From the great pool of patients formerly classified as essential hypertensives, one is now able to delineate properly, prognosticate accurately and treat better such widely diverse pathologic states as pheochromocytoma, Cushing's syndrome, adrenogenital syndrome, coarctation of the aorta, polycystic kidney disease, chronic glomerulonephritis, unilateral kidney disease, and polycythemia vera. Before separation of each of these into proper niches, one factor was shared commonly; namely, hypertension. It is to be hoped that other specific causes of elevated arterial pressure may be defined more accurately so that definitive therapy may be instituted. A step in that direction, meager though it be, is the grouping together of patients exhibiting similar characteristics. The present report outlines the manner in which hypertension is classified on the Research service of the Cleveland Clinic.

Method of Study

History and Physical Examination

In arriving at a diagnosis of the type of hypertension existing, analysis of the time of onset and duration of high blood pressure is important. A patient who is first found to have hypertension at the age of 50 probably has a quite different disease from one who is hypertensive at 20. The true age of onset can usually be determined by careful interrogation of all previous examiners for life insurance, school, athletic endurance, draft boards, etc.

Family history should be carefully explored. In those cases where heredity is a factor, it is not unusual that the type and course of the disease is similar throughout a family.

Since the cerebral blood vessels are not easily examined, one must depend upon symptoms and signs of cerebral vascular insufficiency. These have been recently reviewed by Taylor and Page,[5] and consist of occipital and nuchal pains, vertigo, paresthesia, paresis and paralysis (transient or permanent), and nosebleeds.

The most valuable index of cardiac status in the highly emotional, hypertensive patient is not dyspnea, palpitation, or substernal distress, but rather an estimate of the ease with which he can carry on daily activities.

Manifestations of hyperactivity of the autonomic nervous system must be noted. The most common are a diffuse blotchy red blush over the neck and upper thorax, excessive perspiration, lacrimation and peristalsis. There are episodes of tachycardia and wide fluctuations of blood pressure.

As for the physical examination, the most important single feature is inspection of the ocular fundi. A careful estimate of degree of arteriolar constriction and sclerosis of hemorrhages, exudate and papilledema, should be recorded (Mann and Taylor).[6] Appraisal of the degree of medial sclerosis of the peripheral arteries and the presence or absence of pulsations in the vessels of the legs, are diagnostic aids which are often overlooked.

Laboratory Studies

The electrocardiogram utilizing the standard limb and precordial leads, and the teleoroentgenogram as suggested by Ungerleider and Clark[7] for the measurement of cardiac size, are adequate for establishing the degree of cardiac disease.

The renal vascular bed not only comprises 20 per cent of the body's arterioles, but lends itself admirably to examination. In lieu of elaborate clearance tests which record renal blood flow, and filtration rate, the Addis examination is the best measure of renal vascular integrity. The latter measures tubular function by establishing ability to concentrate urine. It allows quantitative measurement of proteinuria, cylindruria, hematuria, and pyuria. Intravenous urography is a rough measure of diodrast clearance, and often excludes or demonstrates anatomical disease of the urinary tract. Occasionally cystoscopy and retrograde pyelography are necessary to account for unexplained pyuria or hematuria.

Nomenclature

These methods have made it possible to separate patients commonly referred to as having essential hypertension into four usually distinct and characteristic groups. (1) Essential hypertension; (2) malignant phase of essential hypertension; (3) hypertensive diencephalic syndrome; and (4) generalized arteriosclerosis with hypertension.

Essential Hypertension

True essential hypertension may be defined as a disease of unknown causes characterized by persistently increased peripheral resistance due to arteriolar constriction with cardiac augmentation which leads to progressive arteriolar sclerosis. It usually begins in the late teens or early twenties. Initially there are transient elevations of pressure without demonstrable vascular disease. After five or ten years, the blood pressure, both systolic and diastolic, is consistently elevated. The retinal arterioles by this time may show narrowing but little, if any, sclerosis. The results of other examinations are often within normal limits. Within the succeeding decade arterial pressure becomes more sharply

and constantly elevated. Retinal arteriolar constriction is supplemented by sclerosis. The left ventricle of the heart and renal vascular beds fall short of normal functional capacity. In the next ten years, that is by the fifth or sixth decades, symptoms of vascular incompetence appear and insufficiency of cerebral, cardiac, and renal vascular beds can be demonstrated easily.

This disease generally lasts twenty to thirty years. It usually becomes a problem to the physician and patient only in the last ten to fifteen years of its course. There are deviations from the typical course; an occasional patient dies at 25 years of age or earlier of congestive heart failure or cerebral hemorrhage. Some may have hypertension for fifty years and experience a normal life expectancy. However, it is fairly safe to say that a patient with true essential hypertension does not survive past the age of 60.

Malignant Phase of Essential Hypertension

The malignant phase of essential hypertension is a clinical diagnosis. It is based upon the presence of hypertensive vascular disease with papilledema and hemorrhagic retinopathy. It may appear at any age from 7 to 50, unheralded and lightening-like in a person without known vascular disease. Usually, however, it is engrafted upon a pre-existing essential hypertension and rarely upon hypertensive diencephalic syndrome. It occasionally complicates arteriosclerosis, but this is the result of advanced nephrosclerosis and is often comparatively benign.

In addition to the retinal lesions, there is evidence of extensive cardiac and renal change as the result of fulminant necrotizing arteriolitis. Death in malignant hypertension is usually due to renal failure, although some are attributable to congestive heart failure, cerebral hemorrhage, and rarely coronary thrombosis with myocardial infarction.

The course of this phase of the disease varies from one to five years, more often the shorter period.

Hypertensive Diencephalic Syndrome

Hypertensive diencephalic syndrome was described by Page (1938).[8] It usually appears in women who have great emotional sensitivity. The blood pressure is highly labile. The most characteristic sign is the appearance of a diffuse, blotchy red blush over the neck and upper thorax with any emotion. There is excessive lacrimation and perspiration, particularly palmar. Hyperperistalsis is always present with emotion and is often audible. Tachycardia is frequent and with the elevated basal metabolic rate which is found among hypertensive patients, leads to a diagnosis of thyrotoxicosis. Thyroidectomy, which is often performed, has no value.

In spite of blood pressures that are intermittently extremely variable (250/150 to 130/80 mm.Hg) the course of this disease is prolonged. Vascular disease may be minimal at 55 or 60 years of age. The patients usually die eventually of cerebral hemorrhage and only rarely, of subsequent malignant hypertension and renal failure.

To this group may be added certain highly emotional persons frequently of Jewish or Southern European extraction who show all of the signs and symptoms mentioned except the characteristic blush. Such patients have a more striking component of hyperactivity of the intestinal tract. They complain of gaseous dyspepsia, epigastric pain, functional constipation and diarrhea. The course is even more kindly as far as vascular disease is concerned, and more unpredictable as to variations in blood pressure. Tension may be extreme (240/150 mm.Hg) for a few weeks or months; later with the advent of some degree of serenity, it can be normal.

Generalized Arteriosclerosis with Hypertension

Generalized arteriosclerosis with high blood pressure makes its appearance at approximately 50 years of age. Documentary evidence of the onset is particularly important in this group. Hypertension may be discovered during routine examination; or the patient may present himself for examination because of headache, giddiness, or fatigue. Elevation of blood pressure is primarily systolic; however, at times, the diastolic pressure may be as high as 120 or 130 mm.Hg. The pulse pressure nevertheless is invariably great and usually exceeds 100. The pressure is further characterized by its lability. The retinal arterioles show predominate sclerosis with minimal or absent constriction. The peripheral arteries are usually thickened and tortuous. A chest film will indicate tortuosity, elongation and often calcification of the aorta. Depending upon the degree and duration of hypertension, the heart shadow shows evidence of left ventricular hypertrophy.

Kidney function is, as a rule, moderately impaired so that the Addis test shows a maximum ability to concentrate urine to a specific gravity of about 1.020; the urea clearance is approximately 50 per cent of normal and there is a trace of albuminuria.

This condition usually responds well to any therapy which decreases cardiac output, be it bed rest, sedation, reduction of body weight, or relief of headache, giddiness, or fatigue. The blood pressure can generally be maintained at or near normal levels by diligent application of any of the above remedies. Should the patient die of the disease, it is from cerebral hemorrhage or coronary thrombosis and at 65 to 90 years of age. Many succumb to carcinoma or infectious diseases.

Observations

The lability of pressure and the ease with which it can be reduced in several of these conditions may account in part for the frequency with which favorable effects are reported from treatment in "essential hypertension." To test this possibility, 600 consecutive patients with hypertension were classified carefully and the results of treatment analyzed in each group.

Of the 600 hypertensive persons, 320 (53.3 per cent) had essential hypertension. The average age of 237 (39.6 per cent) was 44.3 years, all of whom

had well established hypertensive disease. The remaining 76 (12.7 per cent of the total) averaged 34.8 years of age and had early essential hypertension or were in the stage in which blood pressures were labile and above normal inconstantly. The sex distribution was 57 per cent men and 43 per cent women. There were 39 or 6.5 per cent who had the malignant phase of essential hypertension. Of these 29 were men. This group had an average age of 46.5 years.

Those with the diencephalic syndrome and its allied type of labile hypertension, numbered 47 or 7.8 per cent of the total. All but 5 of these were women. The average age of this group was 41.4 years.

Among those whose hypertension was believed to be secondary to arteriosclerosis, there were 183 patients which comprised 30.5 per cent of the total. The average age of this class was 57.8 years and the sex distribution was about equal with 47 per cent women.

There were 18 patients who fit into none of these classifications. Ten had chronic glomerulonephritis, 1 polycystic kidney disease, 1 chronic pyelonephritis, 5 simple vasomotor lability and 1, Kimmelstiel-Wilson's disease.

Thus, of these 600 patients 51 per cent had blood pressure which varied spontaneously or could be reduced with ease by many simple measures. This large group is therefore unsuitable for any study which depends upon changes of arterial blood pressure as the only method of measuring the results of treatment.

Comment

The analysis presented in no way detracts from the brilliant results which follow certain kinds of therapy offered to patients with severe essential hypertension or the malignant phase of the disease. Various types of sympathectomies have aided and prolonged the lives of hundreds of patients. Thiocyanate alone and in conjunction with sedatives has relieved distressing symptoms such as headache so that otherwise disabled people can lead useful lives. Dietary programs that sharply restrict the intake of sodium have been gratifyingly effective in many cases of severe vascular disease. If these measures were always effective, however, the incidence of early death from hypertension should have receded rather than increased.

The appearance, undoubted though inconsistent, of good results from such varied methods of treatment poses a problem. The problem is to establish means for selecting those patients who will respond to a particular type of treatment in a predictable manner. When this can be done, much time, effort and expense will be saved, and what is more important, such knowledge could well lead to further clarification of the mechanisms responsible for high blood pressure and its attendant blood vessel disease. Progress may be retarded if approximately 50 per cent of the patients with essential hypertension, whose blood pressures are inconstantly elevated are included in therapeutic studies whose results depend upon measured reduction of blood pressure.

References

1. Metropolitan Life Insurance Company estimation of mortality due to diseases of the heart and blood vessels, 1946.
2. Taylor, R. D., Corcoran, A. C., and Page, I. H.: Menopausal hypertension; a critical study. Am. J. M. Sc. **213**:475-476 (April) 1947.
3. Fishberg, A. M.: Hypertension and Nephritis, ed. 4 (Philadelphia: Lea and Febiger, 1939) p. 571.
4. Ayman, D.: Evaluation of therapeutic results in essential hypertension; interpretation of symptomatic relief. J.A.M.A. **95**:246-249 (July 26) 1930.
5. Taylor, R. D., and Page, I. H.: Signs and symptoms of impending cerebral hemorrhage. J.A.M.A. **127**:384-389 (Feb. 17) 1945.
6. Mann, M., and Taylor, R. D.: Significance of ocular fundus changes in hypertension. J. Indiana M. A. **38**:125-128 (April) 1945.
7. Ungerleider, H. E., and Clark, C. P.: Study of transverse diameter of heart silhouette with prediction table based on teleoroentgenogram. Am. Heart J. **17**:92-102 (Jan.) 1939.
8. Page, I. H.: Syndrome simulating diencephalic stimulation occurring in patients with essential hypertension. Am. J. M. Sc. **190**:9-14 (July) 1935.

VIRUS PNEUMONIAS

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UNTIL comparatively recently pneumonias have been classified on a pathologic or anatomic basis, the most common designations having been lobar pneumonia and bronchopneumonia. In the twentieth century, with the isolation and identification of pyogenic bacteria as causative agents, the diagnosis and classification of the pneumonias was further clarified.

The introduction of the sulfonamides and penicillin, which have specific effects on several of the bacterial pneumonias, represented a further forward step. However, the fact that many pneumonias, including those which are now considered to be due to viruses, do not respond to these preparations has raised additional problems. Furthermore, the more frequent use and the improved technics of roentgenograms of the chest have revealed that there are many previously unrecognized types of pneumonia.

Reasons for the lack of interest in pneumonias caused by viruses have been summarized by Reimann:[1] (a) the high incidence in mortality rate of the bacterial pneumonias demanded precedence of interest; (b) the viral infections of the respiratory tract by contrast were of lesser importance; (c) studies were hampered by technical difficulties of research on viruses and a lack of suitable experimental animals; (d) the pulmonary lesions of viral infections are often obscured at necropsy by bacterial invasion, and (e) many pulmonary lesions were undetected because roentgenography in the past was not generally used in mild diseases.

Pneumonias of Known Virus Origin

Measles pneumonia. Pneumonia occurs not infrequently in patients with measles, and roentgenologic and pathologic findings are compatible with those found in other virus pneumonias.

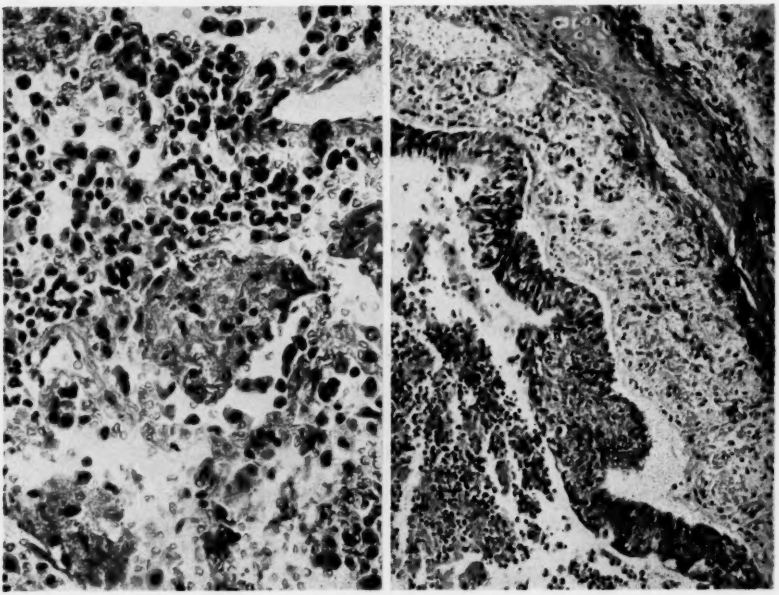
Variola pneumonia. The basis for the pneumonic lesion in patients with variola who develop pneumonia is the underlying infection. This now seems clear, though in the past there was confusion because of the secondary invasion by pyogenic bacteria. Further evidence of the virus causation is offered by the interesting work of Howat and Arnott,[2] who reported a group of patients who developed pneumonia following contact with variola but did not develop variola itself.

Vaccinia pneumonia. Typical virus pneumonia can follow vaccination for smallpox in human beings. Lillie and Armstrong[3] have demonstrated the same reaction in animals.

Varicella pneumonia. Cases of pneumonia associated with chickenpox have been reported.[4,5] Waring *et al.*[6] have described the pathologic picture of virus pneumonia in the autopsy of an adult with chickenpox and pneumonia.

Pneumonia of lymphocytic choriomeningitis. Several authors have reported cases of a typical virus type of pneumonia proved pathologically in patients with lymphocytic choriomeningitis.

Influenzal pneumonia. Influenza has been recurring in pandemics and epidemics for centuries. Secondary invasion by bacteria has caused confusion in spite of the fact that a virus was thought to be the cause of the pandemic of 1918. However, with the discovery of influenza virus A and B, proof has become available of the existence of a true influenzal virus pneumonia. Furthermore, the pathologic picture of pneumonia accompanying endemic and epidemic influenza is not unlike that of other virus pneumonias.



(*a*) (*b*)

FIG. 1. (a) Virus (primary atypical) pneumonia, demonstrating interstitial pneumonitis with mononuclear infiltration (x 200). Death occurred on the fourteenth day of illness. (b) Same case, showing ulceration and squamous hyperplasia of mucous membrane of a bronchiole with dilatation and mononuclear infiltration of its wall (x 70).

It is not known whether the pandemic of 1918 was due to influenza A virus or influenza B or to an as yet unidentified strain. In any event, both A and B influenza occur in endemic form as well as in epidemics. In the recent epidemics they have occurred with the following frequency: influenza A, approximately every two to three years; influenza B, approximately every four to five years. The last major outbreak of influenza B was in 1945, and a mild epidemic of influenza A occurred in the spring of 1947.

A vaccine containing influenza virus A and B has been prepared and used to some extent. It apparently confers specific immunity. However, its use against influenza and its complicating pneumonia in the population at large is not as yet recommended by most authorities because (1) the period of protection may not extend beyond one season, and (2) the disease is now generally mild and of comparatively low incidence and the epidemic is over so rapidly that effective mass immunization cannot be accomplished within one week's time required for the vaccine to become effective. On the other hand, vaccination is generally considered desirable for the protection of elderly or debilitated individuals and for industrial, institutional, and essential public service personnel. The use of the influenza vaccine has proved[7,8,9,10,11] disappointing in several recent instances due to the fact that the epidemics were complicated by previously unrecognized substrains.

Viruses of the psittacosis group. The transmission of virus diseases from birds to man is widely recognized in psittacosis, or parrot fever, which results in a typical pneumonia. Not only may members of the parrot family, which includes canaries and finches, infect man, but so may other species of wild or domesticated birds such as pigeons, doves, and barnyard fowl. The mortality rate from psittacosis has been as high as 40 per cent, especially in older age groups. The diagnosis can be confirmed by complement fixation tests, which the National Institute of Health in Washington, D. C., has cooperated in performing. Some cases have been successfully treated with penicillin.

Pneumonias of Probable Viral Origin

In this group are included (1) pneumonia of infectious mononucleosis, (2) pneumonia of erythema multiforme exudativum, and (3) certain pneumonias of infants. There is growing, although presumptive, evidence that these types of pneumonia are caused by viruses, though as yet the causative agents have not been identified. The roentgenologic and pathologic appearance and the course, however, are similar to the pneumonias of known virus origin.

Other Virus Pneumonias

Primary atypical pneumonia of unknown cause includes a group of pneumonias which has come to occupy an important position in present-day medicine. According to Reimann, there are several reasons for the increased importance: (1) the great reduction in the number of severe bacterial pneumonias by sulfonamide chemotherapy and penicillin, which allowed attention to be given to the milder varieties; (2) their establishment as entities; (3) the more frequent use of roentgenography, and (4) the increase in the number of viral pneumonias in epidemics, particularly among the armed forces during World War II.

The disease, which has come to be called primary atypical pneumonia of unknown etiology and more recently as "virus pneumonia," first came to the attention of the medical profession following a report in 1935 by Major Albert

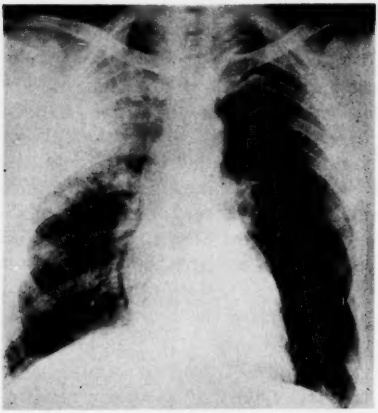


FIG. 2. Case 1. Roentgenogram of chest.

Bowen.[12] He described an epidemic of acute influenzal pneumonitis in several army hospitals in Hawaii. In 1938 Reimann studied similar cases which he grouped into a specific syndrome.

Terminology. Various names have been given to this disease, for example, atypical pneumonia, viral or virus pneumonia, bronchial pneumonia, acute pneumonitis, nonbacterial pneumonia, viroid pneumonia, and sulfonamide-resistant pneumonia. The term "primary atypical pneumonia of unknown cause" is probably in most common use and probably will continue as the accepted term until a specific, consistently demonstrable common agent is found.

Etiology. Presumptive evidence of a causative virus has been presented, but final proof is lacking. Since 1938 a number of agents have been isolated by various investigators, but consistent confirmatory evidence has not been obtained. Examples of such viruses are:

Virus of Stokes *et al.*
Mongoose virus (Wier and Horsfall)
Pneumonia virus of mice (PVM) (Horsfall and Hahn)
Mouse pneumonia virus of Dochez
Guinea pig virus of Rose and Molloy
Cotton rat virus of Eaton
Virus of Rhoads
Virus of Johnson
Cat virus of Howard
Grey lung virus of mice (Andrewes)

The studies of the Commission on Acute Respiratory Disease of the U. S. Army[13] helped to confirm the prevalent belief that primary atypical pneumonia is at least initiated, if not caused, by a filter-passing agent, presumably a virus. These studies also suggested that primary atypical pneumonia is a

severe form of the same infection which is responsible for many of the common mild respiratory illnesses.

Pathology. As in virus pneumonias of known etiology, the histologic picture is fundamentally that of interstitial pneumonitis. In contrast to the inflammatory reaction induced by bacteria, that in primary atypical pneumonia is primarily proliferative. Acute focal bronchiolitis is present with desquamation of the mucosa. Ulceration may be extensive, and squamous metaplasia of the epithelium is often present. The bronchioles are frequently dilated, and their walls are infiltrated chiefly with mononuclear cells. The alveoli may be airless and often contain an exudate of mononuclear clear cells and a few polymorphonuclear cells but not much fibrin. Gross areas of atelectasis and emphysema are often present. (Fig. 1)

Incidence. Military mobilization and other displacements of the population may have increased the incidence since 1941. Virus pneumonias outnumbered all other forms of pneumonia occurring in the armed forces during the war. The disease, as noted by Reimann,[14] " . . . seems to occur in two forms, one consisting of severe, isolated, nonseasonal, sporadic cases, the other, far more common, in epidemic form probably consisting of disease characterized by mild respiratory tract infection, commonly called colds, grippe, viroid, pharyngitis, and influenza and their accompanying severer pneumatic forms."

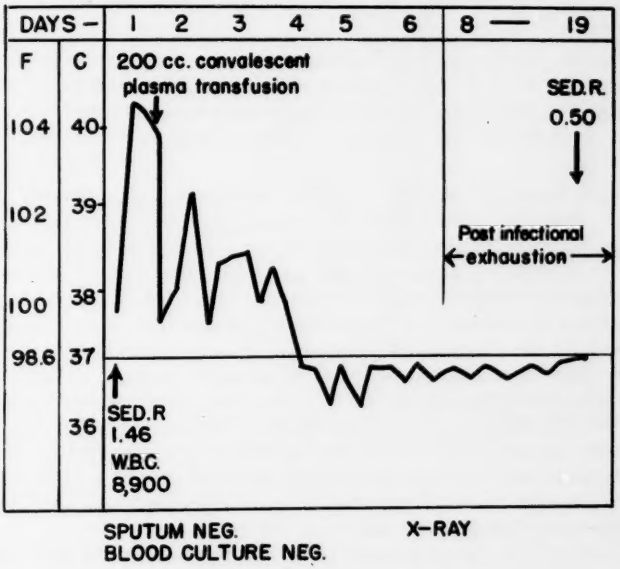


FIG. 3. Case 1. Chart of temperature, laboratory observations, and course.

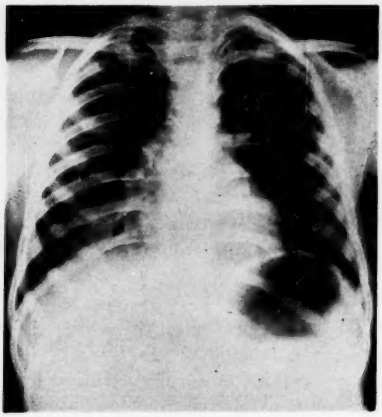


Fig. 4. Case 2. Roentgenogram of chest.

Incubation period. The incubation period is variable. The usual average is believed to be from seventeen to nineteen days with ranges of from one to twenty-six days.

Immunity. Little is known of immunity. Cases of known recurrences have been seen. (We have treated 1 patient with initial illness and two recurrences within a four-year period.) Inasmuch as the exact etiologic agent is not known, however, recurrences may be due to a different agent or strain rather than to the same one.

Clinical features. Primary atypical pneumonia of unknown cause is usually a relatively mild self-limited disease, the onset of which is usually insiduous. Severe respiratory distress is usually absent. The febrile period averages seven to eight days but may last up to forty-five days. There is relative bradycardia, the leukocyte count is normal or only slightly abnormal, and the sedimentation rate is elevated. Characteristic changes may be seen on the roentgenograms. In the diagnosis of pneumonia the x-ray examination is essential; however, the roentgenogram does not demonstrate changes sufficient to distinguish the types of the disease and consequently cannot be relied upon alone to establish the diagnosis of virus pneumonia. The disease does not respond to sulfonamides or antibiotics. Cold hemagglutination occurs late in the course of the disease in about 70 per cent of cases. Agglutination of Streptococcus MG also occurs late in about 70 per cent of cases. The mortality rate is low, estimates generally placing it at about 0.1 per cent.

The onset of the disease is usually less abrupt than that of bacterial pneumonias and the symptoms more varied and with more systemic manifestations. Symptoms in their order of frequency are:

General	
Headache	60-70%
Malaise	60-65%
Chills or chilliness	50-60%
Generalized aches	25-30%
Anorexia	23-30%
Nausea	15-20%
Vomiting	10-15%
Respiratory	
Cough	95-100%
Sputum	80-90%
Sore Throat	23-30%
Pain in chest	10-20%
Dyspnea	5-10%
Epistaxis	5%

Objective findings often parallel symptoms in slowness of appearance and multiplicity.

Fever	95-100%
Nasal congestion	50-60%
Pharyngitis	60-70%
Cervical adenopathy	20-30%
Pulmonary signs	80-90%
Dullness	40-50%
Altered breath sounds	60-70%
Rales	80-90%
Friction rub	5-10%
Fluid	1-2%
Bradycardia	60-70%
Tachycardia	10-20%
Cyanosis	10-15%
Signs referable to the central nervous system	1-2%

Complications. Complications are less common than in bacterial and other virus pneumonias. Their order of relative frequency is:

Bronchiectasis
Pleural effusion
Otitis media
Sinusitis
Thrombophlebitis
Cough fracture
Encephalitis
Lung abscess
Empyema
Pericarditis
Pneumothorax
Massive atelectasis
Hepatitis

In addition to routine differentiation from bacterial pneumonias, other types of virus pneumonia must be considered, such as influenza and psittacosis. Coccidioidomycosis, Q fever, toxoplasmosis, brucellosis, and Loeffler's syndrome must also be eliminated.

Treatment. A specific treatment is not available. Supportive treatment includes bed rest, adequate nourishment and fluids, tepid sponge baths, and cool compresses for the fever, and, especially if delirium is present, cough sedation. Oxygen is indicated for cyanosis. Sodium chloride is administered

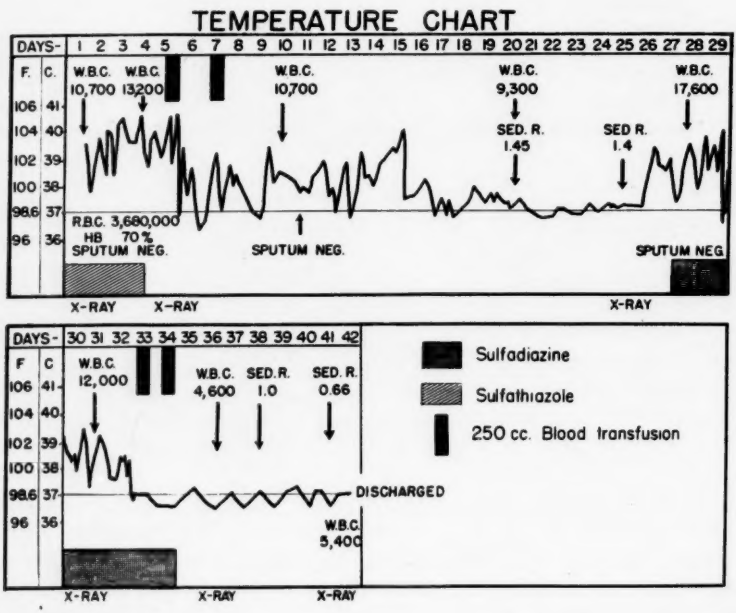


FIG. 5. Case 2. Chart of temperature, laboratory observations, and treatment.

for severe diaphoresis, but antipyretics are generally thought to be contraindicated. Slow resumption of activities in the postinfectional asthenia is required. Sulfonamides or penicillin may be given for bacterial complications or when the diagnosis is uncertain. Convalescent serum has been used. The sedimentation rate is a good guide in convalescence.

Prevention. There are no specific measures of prevention. Avoidance of chilling, fatigue, malnutrition, and exposure to patients having the disease are advisable.

Case Reports

Case 1. A man, aged 41, was admitted to the Cleveland Clinic Hospital after an illness of three days. The onset of symptoms had been gradual, with slight cough and general malaise. The roentgenologic appearance of the pneumonia was essentially of lobar configuration (fig. 2). The clinical characteristics of the illness were, however, those of virus (primary atypical) pneumonia.

The temperature, laboratory observations, and course are shown in fig. 3. A prompt subsidence of the fever and acute symptoms followed the administration of 200 cc. of plasma from a patient convalescing from primary atypical pneumonia. This measure did not, however, prevent a period of postinfectional exhaustion.

Case 2. A boy, aged 11, was admitted to the hospital after sixteen days of fever. Suppression of breath sounds was found over the right middle lung lobe. The roentgenologic examination helped to confirm the diagnosis of pneumonia (fig. 4). Respiratory symptoms did not appear until the third day in the hospital.

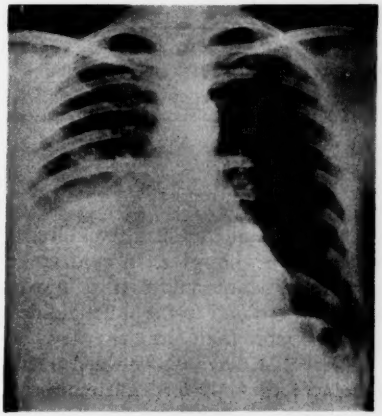


FIG. 6. Case 3. Roentgenogram of chest.

The graphic demonstration of the temperature, laboratory observations, and treatment are shown in fig. 5. The febrile phase of the illness lasted over forty-five days from onset. During this time the physical signs and serial x-ray findings varied considerably in showing shifting areas interpreted as patchy atelectases. The highest titre of the cold agglutinations was 1:560.

Case 3. A housewife, aged 40, had been ill for six days prior to admission with symptoms of alternating chilliness and fever up to 103 F. A nonproductive cough appeared twenty-four hours prior to admission. Roentgenograms of the chest (fig. 6) confirmed the diagnosis of pneumonia in the right lower lung.

The temperature, laboratory findings, and treatment are shown in fig. 7. No response was obtained from penicillin, but dramatic recovery followed the administration of 250 cc. of a standard plasma. The patient was later readmitted, however, with a severe homologous serum jaundice which appeared sixty-two days after the administration of plasma. Recovery from this complication was satisfactory.

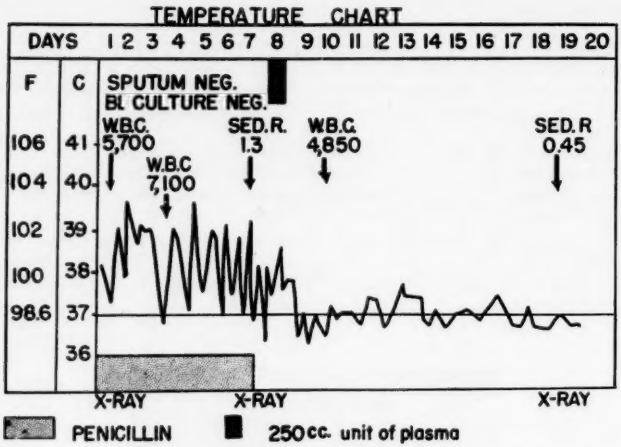


FIG. 7. Case 3. Chart of temperature, laboratory observations, and treatment.

Summary

With the advent of the sulfonamides and penicillin, the frequency of bacterial pneumonias is decreasing; however, in contrast, the incidence of the virus pneumonias is relatively increasing. With the exception of psittacosis, the virus pneumonias do not respond to the sulfonamides or penicillin. Available evidence indicates that more than one virus may be involved in clinically similar pneumonias. Differential diagnosis between bacterial and virus pneumonias is important because the only form of treatment for the virus pneumonias is essentially supportive in nature.

References

1. Reimann, H. A.: Viral pneumonias and pneumonias of probable viral origin. Medicine **26**:167-219 (May) 1947.
2. Howat, H. T., and Arnott, W. M.: Outbreak of pneumonia in smallpox contacts. Lancet **2**:312 (Sept. 2) 1944.
3. Lillie, R. D., and Armstrong, C.: Pathology of generalized vaccinia in rabbits. National Institute Health Bulletin. No. 156, 1-95. 1930.
4. Bullowa, J. G. M., and Wishik, S. M.: Complications of varicella; their occurrence among 2534 patients. Am. J. Dis. Child. **49**:923-926 (April) 1935.
5. Wishik, S. M., and Bullowa, J. G. M.: Complications of varicella; surface complications. Am. J. Dis. Child. **49**:927-932 (April) 1935.
6. Waring, J. J., Neubuerger, K. T., and Greever, E. F.: Severe forms of chickenpox in adults with autopsy observations in case with associated chickenpox and encephalitis. Arch. Int. Med. **69**:384-408 (Mar.) 1942.
7. Francis, T., Jr., Salk, J. E., and Quilligan, J. J., Jr.: Experience with vaccination against influenza in spring of 1947; preliminary report. Am. J. Pub. Health **57**:1013-1016 (August) 1947.

8. Dingle, J. H. Influenza. New England J. Med. **237**:845-852 (Dec. 4) 1947.
9. Editorial. Influenza. New England J. Med. **237**:881-882 (Dec. 4) 1947.
10. Sigel, M. M., Shaffer, F. W., Kirber, M. W., Light, A. B., and Henle, W.: Influenza A in a vaccinated population. J.A.M.A. **136**:437-441 (Feb. 14) 1948.
11. Van Ravenswaay, A. D.: Prophylactic use of influenza virus vaccine. Instance of inadequate protection against influenza A. J.A.M.A. **136**:435-437 (Feb. 14) 1948.
12. Bowen, A.: Acute influenza pneumonitis. Am. J. Roentgenol. **34**:168-174 (Aug.) 1935.
13. Commission on Acute Respiratory Diseases: Transmission of primary atypical pneumonia to human volunteers. J.A.M.A. **127**:146-149 (Jan. 20) 1945.
14. Reimann, H. A.: Acute infection of respiratory tract with atypical pneumonia; disease entity probably caused by a filtrable virus. J.A.M.A. **111**:2377-2384 (Dec. 24) 1938.

HEPATITIS ASSOCIATED WITH UNDULANT FEVER

Report of a Case

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HEPATITIS with jaundice may occur in the course of human Brucella infection although the paucity of published accounts of hepatic involvement in brucellosis indicates that it is uncommon. However, as shown by the autopsy material of Hughes[1] and findings in the liver in specimens obtained by needle biopsy in proved cases of brucellosis,[2] it is evident that pathologic changes in the liver may be a common result of this infection. Jaundice and a positive culture for Brucella organisms in the bile may indicate origin in the gallbladder or duct and are possible manifestations of hepatic involvement. Additional verifications of this theory appear in the experimental work of Amoss.[3] He infected guinea pigs with Brucella organisms and showed that these organisms caused focal lesions in the liver, spleen and lymph nodes. The reactions around these focal areas start as an exudative inflammatory process and lead to the formation of granulomatous nodules which contain a central necrotic mass.

Chaikin and Schwimmer[4] reported a case of hepatitis associated with undulant fever in which jaundice was the first symptom.

A patient who was recently admitted to the Cleveland Clinic illustrates the usual clinical and laboratory evidence of hepatitis associated with brucellosis proved by a positive culture for B. abortus in the blood.

Case Report

A white grocery merchant, age 33, was admitted to the Cleveland Clinic in November, 1947, with the complaint of fever and jaundice. He had become ill in 1943 while on duty at the Great Lakes Naval Training Station. Attacks of chills and fever lasting a few days necessitated hospitalization on four or five occasions and led to his discharge from the service at the end of eight months. The diagnosis was "recurrent catarrhal fever."

Since 1943 he continued to have recurrences of chills and fever, occurring about every one or two months and persisting for a few days. On occasions he received 1 to 2 Gm. of sulfadiazine daily in short courses without apparent relief.

In September, 1947, he suffered pain in the knees, ankles, and finger joints, and approximately a week after the onset developed a high fever and generalized muscular aching. Shortly thereafter he developed gradually increasing jaundice. The urine became dark, but the stools retained a normal color, and there was no pruritus. There was some constipation. At the same time he complained of severe, persistent, aching pains in the right upper quadrant of the abdomen. There was no nausea or vomiting, and his appetite remained good. He had lost approximately 10 pounds. Two days before admission to the Clinic he had perceived some diminution in jaundice, the temperature was lower, and he had become somewhat stronger. This remission of symptoms may possibly be attributed to a daily parenteral dose of streptomycin for four days prior to admission. Several previous short courses of penicillin had failed to alter the course of the disease.

On physical examination the temperature was 98.6 F, pulse 76, and blood pressure 98 systolic, 72 diastolic. The patient appeared chronically ill, and moderate jaundice was present. The only other significant physical manifestation was a tender, smooth liver, palpable two fingers' breadth below the mid right costal margin.

Laboratory examinations revealed hyperbilirubinemia, bilirubinuria, and urobilinogenuria. The icteric index was 32, and the urine showed strongly positive tests for bile and urobilinogen. The stool was normal in appearance. The thymol turbidity was elevated to 7.0 units, and the Hanger test was 2 plus. A diagnosis of undulant fever was made and confirmed by a positive blood culture for B. abortus and a positive blood agglutination in a dilution of 1:2560. A skin test showed a positive reaction to Brucella organisms.

A roentgenogram of the chest showed increased peribronchial markings in both lung fields with a tendency toward nodulation. A cholecystogram faintly demonstrated the gallbladder after two doses of dye. Calculi were not identified.

The patient was referred to his family physician, who had suspected the presence of undulant fever, for treatment. It was recommended that treatment include streptomycin, 0.5 Gm., and sulfadiazine, 1.0 Gm. every six hours, as well as a high carbohydrate, high protein, high caloric diet, and bedrest.

The patient visited the Clinic for follow-up examination eight weeks later. He had received a total of 28 Gm. of streptomycin and a total of 42 Gm. of sulfadiazine, according to the suggested dosage schedule. His only complaint was some residual tightness of the finger joints but no pain. The fever had disappeared, and the jaundice had subsided a few days after institution of treatment. The liver was no longer palpable or tender.

Laboratory examinations at this time revealed a slight bilirubinuria, and two specimens of urine were negative for urobilinogen. The icteric index was 5. Slight elevation of thymol turbidity (5.3 u.) persisted, as did a mildly positive Hanger test (2 plus). In the absence of jaundice a bromsulfalein excretion test was made and found to be normal. Blood culture was negative. Undulant fever agglutination of the blood was 1:80. Culture and microscopic analysis of bile obtained by duodenal drainage was negative. A cholecystogram revealed a normally functioning gallbladder without calculi.

The patient was advised to continue with the previously suggested diet and a modified rest schedule because of the continued slight elevation of the thymol turbidity and positive Hanger test.

The source of infection in this patient cannot be stated with certainty. He had lived on a farm until the age of 18 years. Unpasteurized milk and its products had been used. He had also worked as a meat cutter during the past four years.

The diagnosis of undulant fever in this case was confirmed both by a positive blood culture and high blood agglutination titer. A diagnosis of hepatitis seems justified in view of the enlarged tender liver, jaundice, bilirubinuria, urobilinogenuria, normal stools, elevated thymol turbidity, positive Hanger test, and subsequent normal cholecystograms. A course of streptomycin and sulfadiazine given simultaneously was followed by the disappearance of the Brucella organisms from the blood stream, the lowering of the blood agglutination titer, disappearance of the jaundice, and improvement of the liver function.

References

1. Hughes, M. L.: Mediterranean, Malta, or Undulant Fever (London and New York: Macmillan and Co., 1897).
2. Hoffbauer, F. W., and Spink, W. W.: Biopsy of liver in patients with active brucellosis; description of hepatic lesions. J. Lab. and Clin. Med. **32**:315-316 (March) 1947.
3. Amoss, H. L.: Localization of Brucella. Internat. Clin. **4**:93-98 (Dec.) 1931.
4. Chaikin, N. W., and Schwimmer, D.: Hepatitis in course of Brucella infection. Rev. Gastroenterol. **10**:130-132 (March-April) 1943.

GLYCOSURIA: MECHANISM AND EVALUATION

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Research Division

GLYCOSURIA has, until recently, been thought of in terms of a "renal threshold" by which glucose is retained or excreted according to its concentration in blood. Useful as it has been, this explanation is physiologically unsound (Govaerts and Muller,[1] Mirsky and Nelson).[2] Furthermore it does not resolve clinical problems to which newer concepts of glycosuria apply directly. Hence, the clinician has often had to lead his glycosuric patient through a maze of glucose tolerance tests, measurements of arterial (capillary) and venous blood sugar, and even changes of diet, only to emerge with an insecure conclusion.

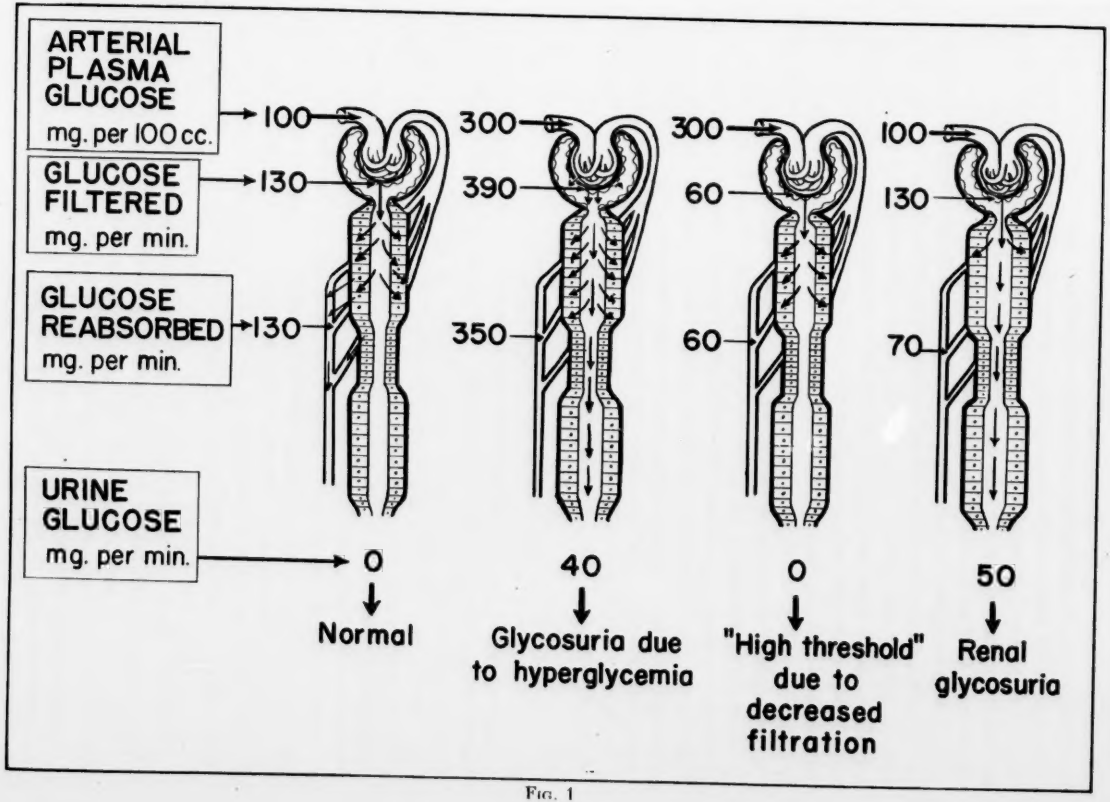
The purpose of this paper is to describe the mechanism of glycosuria as it applies to clinical problems, and to suggest a procedure which may aid in establishing the nature of glycosuria in doubtful cases.

Mechanism of Glycosuria

Formation of urine begins with the outpouring through glomerular capillaries of an ultrafiltrate of plasma. About 1200 cc. of blood, containing 650 cc. of plasma, pass through the kidneys and over the glomerular capillary bed per minute. The hydrostatic pressure furnished by the heart squeezes out from the 650 cc. of plasma about 130 cc. of filtrate. This filtrate consists of plasma water and of the substances dissolved in it. Among these is glucose. Consequently (fig. 1) at a plasma glucose concentration of 100 mg. per 100 cc., the rate of glucose filtration is 130 mg. per minute.

The next step in urine formation is selective reabsorption. This consists in a transfer from the tubule back into the blood of most of the substances present in the filtrate; substances which are not reabsorbed are excreted in urine. Some substances, such as creatinine and inulin are not reabsorbed at all and others only partially. The reabsorption of urea, for example, is passive and partial. It depends on the movement of this highly diffusible substance back into the blood together with the 129 cc. of water reabsorbed from the filtrate. Some of the amino acids, vitamin C, phosphate and sulfate, are actively reabsorbed up to a certain maximum capacity. Thus, the amounts of these substances present in urine remain small until the capacity for active reabsorption is exceeded by an increase in the rate at which they are filtered from blood.

In the case of glucose, reabsorption is active and, normally, virtually complete. The enzymes in cells of the upper part of the proximal convoluted tubules couple glucose with phosphate at the luminal surface of the cell and uncouple the hexosephosphate at the basement membrane, (Marsh and Drabkin).[3] This discharges the glucose into the renal interstitial fluid from which it is carried off in the peritubular blood capillaries. The process can be schematized as a system of carrier belts (fig. 1).


ARTERIAL PLASMA GLUCOSE
mg. per 100 cc.
GLUCOSE FILTERED
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mg. per min.
100
130
130
0
Normal
300
390
350
40
Glycosuria due to hyperglycemia
300
60
60
0
"High threshold" due to decreased filtration
100
130
70
50
Renal glycosuria

FIG. 1

When, for example, the plasma arterial concentration of glucose is tripled and the filtration rate remains unchanged, the amount of glucose presented for filtration becomes 390 mg. per minute. This load of glucose is more than the tubule cells can transfer through the carrier system, which picks up as much as it can and allows the remainder to pass on down the tubule. Here a small fraction may enter into the cells of distal part of the convoluted tubule and be deposited as glycogen. But the bulk of it passes on into the urine. The normal person would, in this circumstance, reabsorb from 300 to 350 mg. per minute and excrete from 40 to 90 mg. per minute. A further increase of blood sugar to 400 mg. per 100 cc. will raise the amount filtered to 520 mg. per minute. The amount excreted in the urine will then increase to from 160 to 220 mg. per minute, while the amount reabsorbed remains constant at 300 to 350 mg. per minute. The amount reabsorbed per minute is therefore at a peak level as Tm_G, where T = tubule, m = maximum and G indicates glucose. The normal average of this function in women is 300 and in men 350 mg. per minute.

Onset of glycosuria is normally dependent on an excess of glucose load (amount of glucose filtered per minute) over the glucose reabsorptive capacity. The latter is a function of the enzymatic activity of tubule cells. But the glucose load depends on arterial plasma glucose concentration and on the rate of glomerular filtration. Hence, there are three factors to be considered in the evaluation of glycosuria. These are (a) plasma glucose content (b) rate of glomerular filtration and (c) reabsorptive capacity of the tubules.

Glycosuria and Hyperglycemia

Glycosuria during hyperglycemia is the result of an excess of renal glucose load (plasma glucose concentration times rate of glomerular filtration) over glucose reabsorptive capacity. As such, it occurs in a wide variety of conditions associated with hyperglycemia. The chief of these is diabetes mellitus, but transitory emotional glycosurias, transient glycosuria after head injury, meningitis and other conditions must be included. The diagnosis of these is not germane to the present topic. However, in considering them, it is important to remember that venous blood sugar content is usually lower than arterial and that arterial content determines the presence or absence of glycosuria. Arteriovenous blood sugar differences can be minimized by heating the forearm for thirty minutes in a water bath at 40° C. before sampling the venous blood which is thus arterialized. Finger-puncture (capillary) blood can be taken as equal to arterial.

So-called "high threshold" diabetes is a problem of serious concern. An increase in apparent threshold may result from (a) decrease in the rate of glomerular filtration, so that the glucose load is not increased beyond reabsorptive capacity as the result of hyperglycemia or (b) from an actual increase in reabsorptive capacity beyond the normal maximum.

Experimentally, reabsorptive capacity for glucose is increased in dogs by administration of thyroxin (Eiler, Althausen, and Stockholm),[4] but human kidneys are apparently less responsive to this sort of stimulation than those of dogs (Corcoran, Taylor, and Page).[5] Indeed, hyperglycemia in hyperthyroid-

ism is not infrequently associated with glycosuria. A recent preliminary report (Farber, Berger, and Earle)[6] demonstrates unusually high glucose reabsorptive capacities (401-460 mg. per minute) in a group of middle aged women with diabetes (normal 300 mg. per minute). This work implies that prolonged hyperglycemia may stimulate reabsorption by a sort of work hypertrophy. This view is in line with clinical experience and accords with one of the observations (Case 4) presented in Table 1.

Unfortunately, the "high renal threshold" of patients suffering from diabetes is often not the result of an increased reabsorptive capacity, but rather due to degenerative vascular disease which decreases the rate of glomerular filtration more than it damages tubules. This vascular disease may consist in renal arteriolar and arterial sclerosis, which decreases renal blood flow, filtration pressure and filtration rate and, consequently, tubular glucose load during hyperglycemia. Or the same may result from deposition of hyaline between the glomerular capillaries (intercapillary glomerulosclerosis). An example of this sort is shown in Table 2, Case 5, in which the estimation of glomerular filtration rate and glucose reabsorption is made during hyperglycemia in a diabetic with decreased renal function. An extreme form of this type of "high threshold" is sometimes seen in patients who are aglycosuric during diabetic coma because glomerular filtration has been sharply decreased by dehydration and hypotension.

TABLE 1

	Arterial Glucose	Glomerular Filtration	Glucose Filtered	Glucose Excreted	Glucose Re-absorbed	Tm_{D-1}	Tm_{PAH}
	mg. per 100	Rate cc/min.	mg. per min.	mg. per min.	mg./min.	mg./min.	
Normal	100	130	130	0	130		
Male	300	130	390	40	350	52	80
Female	300	120	360	60	300	40	60
Case 1	62	100	62	0.1	61.9		
Renal Glycosuria	110	101	112	3	109		
Glomerulonephritis	285	107	305	65	240		
(male)	495	94	466	230	236	35.8	
Case 2	87	110	95	50	45		
Renal Glycosuria	144	117	170	90	80		
(female)	231	134	310	215	95		
	338	112	380	285	95	66	
Case 3	70	145	102	14	88		
Renal Glycosuria	125	122	153	50	103		
(male)	240	123	295	130	165		
	254	143	364	158	206		103
Case 4	495	126	623	165	458		81
Diabetes Mellitus (female)							

Mean normal values in 3 patients with renal glycosuria and in 1 with "high threshold" diabetes. The methods used have been described elsewhere (Corcoran, Taylor, and Page).[7]

TABLE 2

	Blood Sugar mg. per 100 cc.	Urea Clearance C_m. cc. per min.	Estimated Glomerular Filtration cc. per min.	Estimated Glucose Load mg. per min.	Glucose Excreted mg. per min.	Glucose Reabsorbed mg. per min.
Normal	100	75	125	125	0	125
Case 3 (Table 1)	60	90	150	90	5	85
Case 5						
Diabetes	300	20	33	99	0	99
Glomerulosclerosis	500	20	33	166	15	151

Examples of estimation of glucose reabsorption from urea clearance and arterialized blood sugar content in a normal subject, in a case of renal glycosuria (Case 3) and in a patient with intercapillary glomerulosclerosis incident to diabetes mellitus.

Renal Glycosuria

Theoretically, renal glycosuria might sometimes result from an untoward increase in glucose load due to increased glomerular filtration. Practically, this does not occur, because of the relative stability of glomerular filtration rate. Rather, renal glycosuria is an expression of decreased reabsorptive capacity, which may be focal and due to relative failure of the enzyme system n some tubules, while it is relatively intact in others, or to a diffuse failure in all the nephrons.

Glycosuria due to diffuse renal tubular damage occurs in nephroses due to heavy metals (lead, uranium, dichromate) in which the initial injury is tubular rather than glomerular. The coincidence of normal glucose load with decreased reabsorptive capacity results in glycosuria which tends to diminish as renal damage increases and glomerular rate falls. Phloridzin glycosuria is apparently due to a fixation of the glucoside on the enzyme system which blocks the transfer of glucose, but does not destroy the cell. Clinically, minor glycosuria due to focally inadequate tubules appear during chronic glomerulonephritis, or sometimes during recovery from acute glomerulonephritis. Its presence indicates that here and there is a nephron the tubule of which has not recovered its function as rapidly as has the attached glomerulus. Observations in one such patient are summarized in Table 1, Case 1. In this patient, who has a history of glomerulonephritis in remission, the levels of renal blood flow and glomerular filtration were normal. There was minor renal glycosuria at normal blood sugar levels and definite, and approximately equal impairment of the discrete tubular functions of glucose reabsorptive and diodrast secretion. A similar type of "renal glycosuria," not identified as nephritic, has been reported previously (Castex, Biasotti, and Patalano).[8] However, significant renal glycosuria is only rarely the result of renal disease. This is because glomerular and tubular functions are usually concurrently damaged so that glucose load decreases at about the same rate as reabsorptive capacity.

The more severe forms of renal glycosuria are apparently caused by a specific familial defect of the function of glucose reabsorption in the renal

tubules. The condition is uncommon. Observations on 2 such patients are summarized in Table 1.

In the one patient (Case 2) reabsorption of glucose is about 60 per cent complete at normal glucose loads. The maximum reabsorptive capacity as measured during hyperglycemia at high glucose loads is less than one-third normal. In contrast, other measures of renal function (renal plasma diodrast, inulin, xylose and urea clearances) are within normal limits and tubular secretory capacity for diodrast is greater than normal. In another patient (Case 3) glucose reabsorption is about 90 per cent complete at normal loads and reaches an apparent maximum at about two-thirds normal during hyperglycemia. The defect is not as severe as in Case 2. For this reason the patient (Case 3) did not have hypoglycemia during periods of exertion and food-deprivation as did Case 2. Tubular secretion of p-aminohippurate (which measures the same function as diodrast) was beyond, and other renal function tests within normal limits in this patient. Thus, in both these patients the only demonstrable defect in renal function is a selective impairment of the function of glucose reabsorption. They contrast with Case 1 in whom renal glycosuria was a sequal to glomerulonephritis because they do not exhibit depression of tubular secretory function for diodrast or p-aminohippurate.

Others, Friedman, et al.[9] have observed patients with renal glycosuria in whom the *maximum* reabsorptive capacities for glucose were within or above normal limits, although glycosuria was present at even low renal glucose loads. The mechanism of glycosuria in such cases is not as readily explained as in 2 cases here reported. One might suppose that a maximum glucose load sometimes acts as a stimulus to a sluggish reabsorptive mechanism.

Renal glycosuria due to a specific renal defect does not alter health or well-being except as it may predispose to hypoglycemia. Rather, its importance lies in its consequences on employability and insurability. Here, unless it is recognized and proved as such, renal glycosuria can work greatly to the patient's economic disadvantage.

Estimation of Glucose Reabsorption

Proof of renal glycosuria is better achieved by measuring the patient's reabsorptive capacity for glucose than by estimations of intermediary glucose metabolism. Indeed, since renal glycosuria may be present in a patient suffering from diabetes mellitus, estimations of glucose tolerance, may cloud the issue without solving the problem. Ideally, estimation of reabsorption demands concurrent measurements of arterial blood sugar, of glomerular filtration rate and of the urinary excretion of glucose. The first two of these are not readily performed. An expedient which uses means available to most physicians is therefore suggested.

The estimation depends on the fact that the rate of glomerular filtration is, under most circumstances, equal to 1.6 times maximum urea clearance expressed in cc. per minute or 1.2 times urea clearance expressed as per cent of normal.

The patient is prepared for the test by frequent administration of water, in order to maintain urine flows close to 2 cc. or more per minute. Heating the forearm in water at 40° C. for thirty minutes before the test and during arterializes the venous blood. Samples of blood are taken at the beginning of the urea clearance and sixty and one hundred and twenty minutes later. Sugar is measured in each sample and urea in the sixty minute sample. The mean blood sugar level is found for each one hour period of the two hour test. The glucose load for each period is calculated as mg. glucose per cc. of blood multiplied by the glomerular filtration rate as estimated from urea clearance. The urine specimens are analyzed for both glucose and urea. The rate of glucose excretion is expressed in mg. per minute and the difference between this rate and the glucose load is taken as the rate of glucose reabsorption. It is important that nothing be done during the procedure to cause sharp change of blood sugar concentration. The procedure applies to the measurement of glucose reabsorption in renal glycosuria at normal blood sugar levels and in patients with hyperglycemia.

Examples of its application are shown in Table 2. In interpretation, it is important to remember that the demonstration of renal glycosuria raises the question of its possible origin in renal damage. As in Case 1, Table 1, this question is not necessarily answered by a clearance test. A thorough review of the history and examination of other renal functions is therefore necessary before the glycosuria can be dismissed as an unimportant defect.

The approximate level of blood sugar at which glycosuria will *begin* can be calculated from maximum glucose reabsorptive capacity (Tm_G). To do so, Tm_G is divided by the rate of glomerular filtration and multiplied by 100. This gives the concentration of plasma glucose at which the reabsorptive capacity of every nephron is fully engaged. This, in a normal male, is, for example $350/130 \times 100 = 269$ mg. per 100 cc. An allowance of 10 per cent is made for the difference between the sugar contents of plasma and whole blood, thus, $269 \times 90/100 = 242$ mg. per 100 cc. of blood. Finally, an allowance of 25 per cent is made for the concentration at which glycosuria will *begin* because the reabsorptive capacities of the shorter nephrons have been exceeded. In the example, we would have $242 \times 75/100 = 181$ mg. per 100 cc. as the estimated concentration of venous blood sugar at which glycosuria will begin (Nielsen).[10] Since whole blood is used in the clinical test here described, correction for plasma and blood sugar difference is omitted. The calculation, in case 5 (Table 2) becomes $151/33 \times 100 = 458$ mg. per 100 cc. and the probable concentration at the onset of glycosuria is $458 \times 75/100 = 343$ mg. per 100 cc. It should be recognized that such estimates are only approximate.

Summary

Glycosuria is the result of excess of glucose load (plasma glucose content times rate of glomerular filtration) over renal tubular reabsorptive capacity. Glycosuria may be caused by an increase of glucose load during hyperglycemia with normal filtration rate; it may fail to appear in spite of hyperglycemia when glomerular filtration is depressed. The latter mechanism is the

more common cause of so-called "high renal thresholds" in diabetes, although glucose reabsorptive capacity is increased in some patients.

Renal glycosuria is due to a focal or diffuse failure of the enzymatic process of glucose reabsorption. This failure may arise from renal tubular damage, such as occurs in toxic nephrosis or glomerulonephritis, or it may be an isolated specific defect, usually familial.

A method is described for the approximate determination of glucose reabsorptive capacity from urea clearance and concurrent blood and urine sugar.

References

1. Govaerts, P., and Muller, P.: Mechanism of glucose excretion by kidney in diabetic dogs. J. Clin. Investigation **18**:25-30 (Jan.) 1939.
2. Mirsky, I. A., and Nelson, N.: Significance of glycosuria. Arch. Int. Med. **71**:827-835 (June) 1943.
3. Marsh, J. B., and Drabkin, D. L.: Kidney phosphatase in alimentary hyperglycemia and phlorhizin glycosuria. J. Biol. Chem. **168**:61-73 (April) 1947.
4. Eiler, J. J., Althausen, T. L., and Stockholm, M.: Absorption of galactose by renal tubules of dog. Proc. Soc. Exper. Biol. and Med. **56**:67-70 (May) 1944.
5. Corcoran, A. C., Taylor, R. D., and Page, I. H.: Specific renal functions in hyperthyroidism and myxedema. J. Clin. Endocrinol. **7**:801-806 (Dec.) 1947.
6. Farber, S. J., Berger, E. Y., and Earle, D. P.: Effect of diabetes and insulin on glucose Tm. Proc. Am. Soc. Clin. Investigation. J. Clin. Investigation **26**:1180-1181 (Nov.) 1947.
7. Corcoran, A. C., Taylor, R. D., and Page, I. H.: Functional patterns in renal disease. Ann. Int. Med. **28**:560-582 (March) 1948.
8. Castex, M. R., Biasotti, A., and Patalano, A.: Tubular reabsorption in renal diabetes. Rev. soc. argent. biol. **18**:351-357 (July) 1942.
9. Friedman, M., Selzer, A., Sugarman, J., and Sokolow, M.: Renal blood flow, glomerular filtration rate and degree of tubular reabsorption of glucose in renal glycosuria. Am. J. M. Sc. **204**:22-29 (July) 1942.
10. Nielsen, A. L.: On mechanism of glycosuria. I. Acta. med. Scandinav. **130**:219-231, 1948.

DIVERTICULOSIS OF THE COLON

Review of 726 Consecutive Cases

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DIVERTICULA are not infrequently found in the various portions of the gastrointestinal tract. They occur more frequently in the colon, especially in the sigmoid colon, than elsewhere in the gastrointestinal tract. Collins[1] has reported an incidence of diverticula of the colon in 7 per cent of 3000 consecutive barium enema examinations.

Etiology

Diverticula of the colon are blind sacs or pouches branching from the lumen of the colon. While the exact cause is unknown, several theories have been suggested.

The embryologic theory[2] postulates that the bowel develops from a diverticulum. Since the liver, pancreas, cecum and appendix arise as diverticula from the bowel, sporadic secondary diverticula should not be unexpected. Diverticula are found in close relationship to the vessels entering the bowel from the mesentery. At these points of entry into the bowel wall there may be weak spots which herniate with the formation of diverticula.[3] There are also inherent weak areas in the bowel wall which cannot withstand the intraluminal pressure to which they are subjected.[4]

Location

Diverticula occur most frequently in the sigmoid colon but rarely in the rectum. They appear with decreasing frequency from the sigmoid colon proximally to the cecum.

This report is based on a study of 726 consecutive cases of diverticulosis of the colon observed at the Cleveland Clinic. Each patient has had a complete gastrointestinal survey. Cases in which diverticula were merely suspected either clinically or radiologically were excluded. The series includes cases in which diverticulosis of the colon was the only organic abnormality as well as those which manifested other abnormalities of the gastrointestinal tract. In many cases the diverticula had multiple locations (Table 1).

TABLE 1

Location of the Diverticula

	No.	Per Cent
Sigmoid colon	654	90
Descending colon	348	47.9
Transverse colon	121	16.5
Ascending colon	55	7.6
Cecum	10	1.3

Table 2 gives the distribution of the diverticula according to arbitrary divisions of the colon. Diverticula were approximately thirty-five times as common in the left colon as in the right; diverticula of the left colon were fifteen times as frequent as the generalized form.

TABLE 2*

Frequency

	No.	Per Cent
Left colon	662	92
Right colon	19	2
Generalized	45	6

Sex Distribution

The incidence of diverticula of the colon is about equal in the two sexes. Kocour[5] studied diverticula of the colon in 7000 consecutive autopsies and reported the incidence to be 35 per cent higher in women than in men. There is little difference shown in this series, Table 3.

TABLE 3

	No.	Per Cent
Men	398	54.83
Women	328	45.17

Age Distribution

According to most reports diverticula of the colon are rarely observed in persons under the age of 20 and the incidence increases until the age of 60. In this series 55 per cent were between 40 and 60 years old. It is noteworthy that 75 per cent of the total series were 50 years of age or older. There were only 5 patients under 30. The youngest patient was 25 years old (figure).

**For the purposes of this report the right colon includes the cecum and ascending colon, the left colon the transverse, descending and sigmoid portions.*

The Factor of Obesity

It is generally believed that obesity favors the formation of diverticula of the colon. In this series of cases approximately 65 per cent were overweight, 7 per cent were underweight and 28 per cent were within normal limits using standard weight and height charts as a base line.

In 121 of these cases some organic disease of the gastrointestinal tract other than the presence of diverticula of the colon was also found, but this did not alter the percentages significantly.

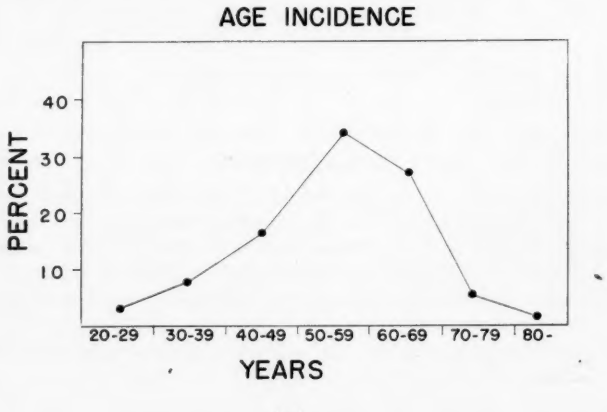
Symptoms

In a series of cases of diverticula of the colon reported by Willard and Bockus[6], only about 50 per cent had symptoms considered related to the presence of the colonic diverticula. Spriggs and Marxer, also cited by Bockus[6] did not find any complaints referable to the presence of diverticula in the colon in 29 of their 100 cases.

It appears logical that symptoms resulting from diverticula of the colon would reflect some alteration in the function or behavior of the colon. The symptoms of which the patients complained followed a remarkably consistent pattern. Predominating in the series were flatulence, constipation, and pain, or abdominal discomfort. They probably indicate an alteration of the large bowel function. When diverticula are found in a patient having complaints referable to the gastrointestinal system however, it cannot be assumed that the symptoms are due to the presence of the diverticula alone.

Bockus[6] states that a history of diarrhea or alternating diarrhea and constipation are common complaints and in his series reported that such a history was present in 25 per cent of their cases. In this series only about 9 per cent gave a history of diarrhea.

The history of constipation or diarrhea is at times difficult to evaluate as the average patient has only a vague idea as to the nature or meaning of these



terms. In our series constipation was diagnosed only in those patients who gave a history of hard, infrequent dry stools or in those who found it necessary to take frequent laxatives in order to obtain any bowel movement. Diarrhea was considered present in those patients who gave a history of repeated or continuous episodes or three or more loose watery stools a day.

The abdominal pain or discomfort of which the patient with diverticulosis complained was often vague and could be poorly localized. It might involve any portion of the abdomen but was usually in the lower abdomen and the left lower quadrant. The pain was not constant and tended to recur. Often there was a history of relief by the passage of flatus or by a bowel movement. The type of pain could be roughly described as sharply stabbing, cramp-like or aching. The location varied and was not necessarily consistent with the anatomical location of the diverticula. A numerical analysis of the type and location in the 404 patients who gave pain as a symptom is shown in table 4.

TABLE 4

Type of Pain

Type	No.
Ache	207
Cramp	137
Sharp	60

Location of Pain

Lower abdomen	122
Left lower quadrant	95
Right upper quadrant	53
Epigastrium	49
Right lower quadrant	35
Left upper quadrant	34
Generalized	26

Whether blood occurs in the stool in uncomplicated diverticulosis has been a matter of dispute. It certainly does not occur frequently. In this series, 36 patients gave a history of passage of gross blood by rectum. On examination some cause other than the diverticula was found in 11; in 25 no other cause was found. Therefore, in only 3½ per cent of the cases in this series could rectal bleeding be attributed to the presence of colonic diverticula.

Other symptoms such as anorexia, nausea, vomiting, weight loss and the passage of mucus in the stools were even less frequent.

Many patients had had one or more abdominal operations. The sigmoid and the descending colon frequently could be palpated as a spastic rope-like cord. Tenderness was common but was usually mild and not accompanied by muscle spasm.

In general the symptoms and physical findings of the patients in this series were like those observed by Collins and Van Ordstrand[7] in their report of 1000 consecutive cases of irritable colon seen at the Cleveland Clinic. In this series the relative duration of the symptoms (eight years) is about the same as in this series (six years); the age and sex incidence were approximately the same, and the complaints almost identical, namely, "gas," abdominal distress or pain, constipation and to a lesser extent nausea and vomiting. We believe that the similarity of the symptoms and the response to treatment are more than coincidental. Doubtless the presence of the diverticula may aggravate the symptoms and may lead to later complications. It seems more logical to suppose that the diverticula are the result of the irritable colon or that they have become larger as a result of the altered function of the large bowel due to the irritable colon.

Table 5 presents the symptoms of the entire series and table 6 the symptoms in those cases in which colonic diverticulosis was the only gastrointestinal abnormality found.

TABLE 5

Symptoms of All Patients (726)

	No.	Per Cent
"Gas"	543	74.8
Constipation	498	68.6
Pain or abdominal discomfort	404	55.6
Abdominal fullness	188	25.3
Nausea	79	11
Diarrhea	68	9.3
Mucus in the stools	41	5.6
Melena	36	4.9
Anorexia	29	4
Average duration of symptoms		5.9 years

TABLE 6

Symptoms in Patients with Colonic Diverticula Alone (605 cases)

	No.	Per Cent
"Gas"	472	78
Constipation	404	66.7
Pain or abdominal discomfort	336	55.5
Abdominal fullness	150	24.8
Nausea	67	11
Diarrhea	53	8.7
Mucus in the stool	31	4.9
Melena	25	4.7
Anorexia	28	4.8

Associated Organic Gastrointestinal Disease

In this series there were 121 patients or 16½ per cent in which organic gastrointestinal disease was found. Gallbladder disease and duodenal ulcer were the conditions most commonly encountered. Although cancer of the gastrointestinal tract is considered rare in association with diverticula of the colon 24 cases were found in this series. In 2 others the diagnosis of cancer of the colon was made clinically and by x-ray but since the patients refused operation the diagnosis was not confirmed. The incidence of the associated gastrointestinal lesions is shown in table 7, and table 8 shows the location of the associated lesions.

TABLE 7

Associated Gastrointestinal Disease

Cholelithiasis	45
Duodenal ulcer	26
Carcinoma	24
Cholecystitis	18
Gastric ulcer	3
Amebiasis	3
Ulcerative colitis	1
Polyp of the sigmoid	1

TABLE 8

Location of Neoplasms

Sigmoid	13
Rectum	4
Hepatic flexure colon	2
Stomach	2
Splenic flexure colon	1
Ileum	1
Jejunum	1

Diagnosis

The diagnosis of diverticulosis should be suspected in any patient over the age of 40 who is overweight, and has a history of long-standing flatulence, constipation and abdominal discomfort or poorly localized pain which tends to be relieved by a bowel movement or by the passage of flatus. The diagnosis is made by exclusion of other possibilities and can be substantiated only by x-ray examination.

Treatment

The treatment of diverticulosis of the colon is aimed first at the determination of the underlying cause of the symptoms and second at the prevention of future complications.

Undue emotional upsets and either nervous or physical exhaustion should be avoided as far as possible. In the obese person weight reduction is desirable. Small weekly or bi-weekly doses of barium sulfate by mouth is often advised, especially in the patients in whom a mild diverticulitis is suspected. The hope is that the barium will fill the diverticula and that this inert substance will prevent further irritation. Barium sulfate should not be given when symptoms indicate partial obstruction or impending obstruction. The diet suggested is of a low residue type with absolute avoidance of seeds, skins and coarse fibers. The treatment of constipation depends upon the adherence of the patient to the principles of bowel management. This includes ample sleep and rest, adequate fluid intake, habit time and the use of one of the bland bulk producing mucilaginous or Karaya gum preparations until the rectum is re-trained to a habit time. When the stool is unduly hard the use of a three ounce oil retention enema before retiring will usually result in a soft stool the next morning. At the beginning of treatment it may be necessary to initiate bowel movement at the habit time by the insertion of a glycerine suppository. Harsh or irritative laxatives and enemas should be avoided. At the beginning of treatment antispasmodics such as belladonna or some related compound and the use of phenobarbital in small doses will aid in the reduction of the spasm of the colon as well as relax the patient. Mild exercise taken out of doors is often beneficial. As improvement takes place in the symptomatology, especially in the constipation, a normal diet may be resumed and the use of drugs discontinued.

The nature of the patient's illness should be discussed with him. Care must be taken, however, not to emphasize the presence of the diverticula because many of these patients have a nervous temperament and are already concerned with their intestinal complaints. The nature of the diverticula, their relative innocuousness, and the simplicity and success of the treatment should be explained carefully so that the patient may have a clear understanding of the problem. The three "Rs" of Kantor are most important: "Reassurance, rest and relaxation." During the first and the most discouraging part of the treatment, the patient should be observed at frequent intervals so he may discuss the problems of treatment and gain encouragement to continue. Even though the condition is not serious it is important, and comfort can be improved and a life of semi-invalidism avoided by patient care. The low incidence of the complications of diverticulosis in those patients who follow proper management should be explained. Brown and Marcley[8] report that in 192 cases of uncomplicated diverticulosis of the colon given medical management above only 1 developed diverticulitis.

Summary

An analysis of the history of 726 cases of uncomplicated diverticulosis of the colon reveals that the symptomatology is essentially the same as that of irritable colon.

Diverticulosis of the colon is an abnormality most commonly observed in middle age. Seventy-five per cent of the cases in this series were over 50 years old. It is

most prevalent in the overweight or obese persons. Sixty-six per cent of this series were in this group.

Cancer of the gastrointestinal tract was found in 3½ per cent of these cases. It was located in the colon or rectum in the majority.

The diagnosis of diverticulosis of the colon is made only by the exclusion of any other lesion of the gastrointestinal tract and by x-ray examination.

The treatment of diverticulosis of the colon is based on the prevention of future complications and on eliminating as far as possible the underlying causes. We believe that the symptoms are due to irritable colon and not to the presence of the diverticula.

The prognosis of patients with uncomplicated diverticulosis of the colon who follow proper management is excellent.

References

1. Collins, E. N.: Roentgen aspects of diseases of colon. Cleveland Clin. Quart. **3**:83-100 (April) 1936.
2. Druek, C. J.: Diverticula and diverticulitis. Rev. Gastroenterol. **4**:134-139 (June) 1937.
3. Reineke, H. G.: Diverticulitis of colon. Ohio State M. J. **40**:939-941 (Oct.) 1944.
4. Bearse, C.: Diverticulosis and diverticulitis of colon in young people. J.A.M.A. **132**:371-373 (Oct. 19) 1946.
5. Kocour, E. J.: Diverticulosis of colon; its incidence in 7000 consecutive autopsies with reference to its complications. Am. J. Surg. **37**:433-436 (Sept.) 1933.
6. Spriggs, E. I., and Marxer, O. A., cited by Bockus H. L. et al.: Gastro-Enterology, Vol. II (Philadelphia: W. B. Saunders Company, 1944) p. 674-708.
7. Collins, E. N., and Van Ordstrand, H. S.: Review of 1000 consecutive cases of irritable colon; its simulation of surgical conditions and treatment. Cleveland Clin. Quart. **8**:67-78 (April) 1941.
8. Brown, P. W., and Marcley, D. M.: Prognosis of diverticulitis and diverticulosis of colon. J.A.M.A. **109**:1328-1333 (Oct. 23) 1937.

APPOINTMENTS

Dr. A. Carlton Ernstene has been appointed head of the Division of Internal Medicine. Dr. Ernstene has been a member of the Clinic staff since 1932 and has been head of the Section on Cardiovascular Disease for many years.

Dr. Roscoe J. Kennedy has been appointed head of the Department of Ophthalmology. He came to the Cleveland Clinic in 1937 to complete a Fellowship, and was appointed to the professional staff in 1938.

Four new appointments to the permanent staff have been made recently. Dr. F. William Sunderman comes to the Clinic as head of the Department of Clinical Pathology. Dr. Sunderman, who has been certified both by the American Board of Internal Medicine and the American Board of Pathology, has been living in Philadelphia where he has been Assistant Professor of Research Medicine at the University of Pennsylvania and most recently Professor of Clinical Pathology and Director of the Laboratory of Clinical Medicine at Temple University Medical School. Dr. Shelby G. Gamble, who is a former Fellow and staff assistant, has been appointed to head the Department of Physical Medicine. During recent years Dr. Gamble has been located in Columbus, Ohio where he was Assistant Professor in the Department of Medicine at Ohio State University College of Medicine and Director of the Department of Physical Medicine at both University and Children's Hospitals in that city. Dr. Charles H. Brown has been made a member of the Department of Gastroenterology in the Division of Internal Medicine. Since leaving the Army Air Forces early in 1946, he has been at the Henry Ford Hospital in Detroit, Michigan. Also added to the staff is Dr. Donald W. Bortz, who after graduation from Jefferson Medical College served successively as Fellow in Medicine at the Clinic and, after a two-year interval in the Navy, as a member of the assistant staff. He has been appointed in the Division of Internal Medicine.

Drs. Earl W. Netherton, U. V. Portmann, John Tucker, and James A. Dickson have been elected as members of the Cleveland Clinic Foundation and the Bunts Institute. All have been members of the staff for more than 25 years. The other professional members are Drs. Thomas E. Jones and Russell L. Haden, who together with the trustees constitute the membership of the Foundation and of the Institute.

BUNTS INSTITUTE

On Thursday, Friday, and Saturday, October 7, 8, and 9, the Bunts Institute will present a continuation course on Diseases of the Digestive Tract. Guest speakers will be Dr. Lester R. Dragstedt, Professor of Surgery at the University of Chicago, who will speak on "Bilateral Vagotomy in Treatment of Peptic Ulcer," and Dr. T. Grier Miller, Professor of Clinical Medicine at the University of Pennsylvania, who will speak on "Intestinal Intubation" and will take part in the Panel Discussion on Saturday. The complete program was published in the July Quarterly. Registration and further inquiries can be addressed to Dr. Edwin P. Jordan at the Cleveland Clinic Building.

ERRATUM

On page 127 of the July, 1948 issue of the Quarterly, top line, the figure .0007 should have been 0.007.

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